

1. (amended) Deacetoxycephalopirin C synthase (DAOCS) having a structure designated by the X-ray co-ordinates of structure A or structure B [herein].

2. (amended) DAOCS in the form of a complex with a metal, [e.g. iron or lead, and optionally in the presence of a substrate and/or a substrate analogue or inhibitor,] having a structure designated by the X-ray co-ordinates [herein] of structure B.

3. (amended) DAOCS as claimed in claim [2] 28, wherein the substrate is selected from the group consisting of penicillin N, penicillin G, 2-oxoglutarate or dioxygen [,and the inhibitor is selected from N-oxalylamino acids, pyridine-carboxylates and nitrous oxide].

4. (amended) [Use of the three-dimensional structure of DAOCS for the modification of] A method of modifying DAOCS or other related 2-oxoglutarate dependent [enzyme] enzymes comprising referring to the three-dimensional structure of DAOCS to select the modification of said enzymes.

5. (amended) [Use as claimed in] The method of claim 4, wherein the related 2-oxoglutarate dependent enzyme is DACS, DAOC/DACS or the oxygenase enzyme involved in the introduction of the 7 $\alpha$ -methoxy group into cephamycin C.

6. (amended) [Use as claimed in] The method of claim 5, [for] wherein the modification of DAOCS, DACS or DAOC/DACS is such that they accept unnatural substrates more efficiently than the wild type enzymes.

7. (amended) [Use as claimed in] The method of claim 5, [for] wherein the modification of DAOCS, DACS, DAOC/DACS is such that they convert natural substrates to pharmaceuticals or useful intermediates in the preparation of pharmaceuticals.

8. (amended) [Use as claimed in] The method of claim 6, wherein the unnatural substrates are penicillins [including penicillin G, penicillin V, 6-aminopenicillanic acid, amoxycillin, or penicillins with a phenyl glycine or p-hydroxyphenyl glycine side chain].

9. (amended) [Use as claimed in] The method of claim 6, wherein the unnatural substrate is a cephalosporin.

10. (amended) [Use as claimed in] The method of claim 6, wherein the unnatural substrate is an amino acid or a peptide.

11. (amended) [Use as claimed in any one of claims] The method of claim 6[-8], wherein [penicillin G, penicillin V, another] unnatural substrate [or penicillin N] is converted to a cephalosporin [or exomethylene cephalosporin].

12. (amended) An enzyme having significant [(as herein defined)] sequence similarity to DAOCS, wherein the side chain binding site of [penicillin N or] DAOC is modified and at least one amino acid residue [and] at [at least] one or more of the following sites [at least one amino acid residue] selected from the group consisting of Thr72, Arg74, Arg75, Glu156, Leu158, Arg160, Arg162, Leu186, Ser187, Phe225, Phe264, Arg266, Asp301, Tyr302, Val303, and Asn304; is changed to another amino acid residue or is deleted[: Thr72, Arg74, Arg75, Glu156, Leu158, Arg160, Arg162, Leu186, Ser187, Phe225, Phe264, Arg266, Asp301, Tyr302, Val303,

and Asn304; and/or at least one additional amino acid residue is inserted within the region 300-311; provided that other residues interacting with the above may be changed in order to accommodate the change in one of the above].

13. (amended) An enzyme having significant [(as herein defined)] sequence similarity to DAOCS, wherein the penicillin/cephalosporin binding site of [penicillin N or] DAOC is modified [and at] at [least] one or more of the following amino acid residues selected from the group consisting of Ile 88, Arg160, Arg162, Phe164, Met180, Thr190, Ile192, Phe225, Pro241, Val245, Val262, Phe264, Ile305, Arg 306, and Arg307; is changed or deleted: [Ile 88, Arg160, Arg162, Phe164, Met180, Thr190, Ile192, Phe225, Pro241, Val245, Val262, Phe264, Ile305, Arg 306, and Arg307; and/or at least one additional amino acid residue is inserted within the region 300-311; provided that other residues interacting with the above may be changed in order to accommodate the change in one of the above].

14. (amended) An enzyme according to claim 12 [or claim 13] which is a [mutant] modification of DAOCS or DACS or DAOC/DACS.

15. (amended) An enzyme [as claimed in any one of claims 12-14] having significant sequence similarity to DAOCS, wherein both the side chain and the penicillin/cephalosporin binding sites of penicillin N or DAOC are modified and at least one of the residues [specified in claims 12 and 13] selected from the group consisting of Thr72, Arg74, Arg75, Ile88, Glu156, Leu158, Arg160, Arg162, Phe164, Met180, Leu186, Ser187, Thr190, Ile192, Phe225, Pro241, Val245, Val262, Phe264, Arg266, Asp301, Tyr302, Val303, Asn304; Ile305, Arg 306, and Arg307 is changed or deleted [and/or at least one additional amino acid residue is inserted within the region 300-311; provided that other residues interacting with the above may be changed in order to accommodate the change in one of the above].

16. (amended) An enzyme as claimed in [any one of claims] claim 12[-15], wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

17. (amended) A [gene] polynucleotide encoding [for] the enzyme of [any one of claims] claim 12[-16].

18. (amended) A micro-organism capable of expressing the [gene] polynucleotide of claim 17 under fermentation conditions.

19. (amended) [Use of] The method of using the micro-organisms of claim 18 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

20. (amended) [Use as claimed in] The method of claim 19, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway [including isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase].

22. (amended) A method as claimed in claim 21 wherein the said other related 2-osoglutarate dependent enzyme or related enzyme is 1-aminocyclopropane-1-carboxylate oxidase, gibberellin C-20 oxidase, flavone synthase, flavanone 3 $\beta$ -hydroxylase, hyoscyamine 6 $\beta$ -hydroxylase, prolyl 4-hydroxylase, prolyl 3-hydroxylase, aspartyl hydroxylase, lysyl hydroxylase, proline hydroxylases,  $\gamma$ -butyrobetaine hydroxylase, enzymes in herbicide resistance mechanisms, clavamate synthase, and oxygenase enzyme involved in the biosynthesis of carbapenems, the [so called] ethylene forming enzyme from *Pseudomonas syringae*, p-

hydroxyphenylpyruvate dioxygenase, [and] or an oxygenase enzyme involved in the oxidation of phytol in human liver peroxisomes.

23. (amended) A method as claimed in claim 21 [or 22] wherein the said other enzyme is modified, by deletion or addition or alteration; at one or more of the sites [defined in claim 12 or 13] selected from the group consisting of Thr72, Arg74, Arg75, Ile 88, Glu156, Leu158, Arg160, Arg162, Phe164, Met180, Leu186, Ser187, Thr190, Ile192, Phe225, Pro241, Val245, Val262, Phe264, Arg266, Asp301, Tyr302, Val303, Asn304; Ile305, Arg 306, and Arg307; or using the following information for the design [or] of an inhibitor: Asp185, His183 and His243 act as ligand to the iron; Arg258 and Ser260 and the Fe bind the 2-oxoglutarate; Met180, Phe225, Leu31 and Val245 are close to the iron binding site; Tyr33, Arg160, Arg162, Phe164, Ile192, Gln194, Leu204, Leu223, Leu215 are important for the construction of the part of the active site binding 2-oxoglutarate; and Arg160 and Arg162 are important for binding an amino acid or peptide derived substrate.

24. (amended) A method as claimed in [any one of claims] claim 21[-23], wherein the said other enzyme is prolyl 4-hydroxylase, prolyl 3-hydroxylase, aspartyl hydroxylase, or lysyl hydroxylase and the inhibitor is to be used for the treatment of human diseases including fibrotic diseases including liver cirrhosis and arthritis.

25. (amended) A method as claimed in [any one of claims] claim 21[-23], wherein the said other enzyme is p-hydroxyphenylpyruvate dioxygenase and the inhibitor is to be used in the treatment of certain genetic disorders.

26. (amended) A method as claimed in [any one of claims] claim 21[-23], wherein the said other enzyme is involved in herbicide resistance and the information is to be used to design new herbicides to overcome the problem of resistance.

**Please add the following new claims:**

27. The DAOCS of claim 2, wherein said metal is iron or lead.
28. The DAOCS of claim 2, wherein said complex includes a substrate.
29. The DAOCS of claim 2, wherein said complex includes a substrate analogue.
30. The DAOCS of claim 2, wherein said complex includes an inhibitor.
31. DAOCS as claimed in claim 30, wherein the inhibitor is selected from the group consisting of N-oxalylamino acids, pyridine-carboxylates and nitrous oxide.
32. The method of claim 8, wherein said penicillins are selected from the group consisting of penicillin G, penicillin V, 6-aminopenicillanic acid, amoxycillin, and penicillins with a phenyl glycine or p-hydroxyphenyl glycine side chain.
33. The method of claim 10, wherein said amino acid is a proteinogenic amino acid.

34. (amended) [Use as claimed in any one of claims] The method of claim 6[-8], wherein [penicillin G, penicillin V, another] unnatural substrate [or penicillin N] is converted to a [cephalosporin or] exomethylene cephalosporin.

35. The method of claim 8, wherein penicillin G, penicillin V or penicillin N is converted to a cephalosporin.

36. The method of claim 8, wherein penicillin G, penicillin V or penicillin N is converted to an exomethylene cephalosporin.

37. The enzyme of claim 12, further comprising the insertion of at least one additional amino acid residue within the region 300-311.

38. An enzyme having significant sequence similarity to DAOCS, wherein the side chain binding site of DAOC is modified and at least one additional amino acid residue is inserted within the region 300-311.

39. An enzyme having significant sequence similarity to DAOCS, wherein the side chain binding site of DAOC is modified and at least one amino acid residue at one or more of the following sites selected from the group consisting of Thr72, Arg74, Arg75, Glu156, Leu158, Arg160, Arg162, Leu186, Ser187, Phe225, Phe264, Arg266, Asp301, Tyr302, Val303, and Asn304; is changed to another amino acid residue or is deleted.

40. The enzyme of claim 12, further comprising the insertion of at least one additional amino acid residue within the region 300-311.

41. An enzyme having significant sequence similarity to DAOCS, wherein the side chain binding site of penicillin N is modified and at least one additional amino acid residue is inserted within the region 300-311.

42. The enzyme of claim 13, further comprising the insertion of at least one additional amino acid residue within the region 300-311.

43. An enzyme having significant sequence similarity to DAOCS; wherein the penicillin/cephalosporin binding site of DAOC is modified and at least one additional amino acid residue is inserted within the region 300-311.

44. An enzyme having significant sequence similarity to DAOCS, wherein the penicillin/cephalosporin binding site of penicillin N is modified at one or more of the following amino acid residues selected from the group consisting of Ile 88, Arg160, Arg162, Phe164, Met180, Thr190, Ile192, Phe225, Pro241, Val245, Val262, Phe264, Ile305, Arg 306, and Arg307; is changed or deleted .

45. The enzyme of claim 13, further comprising the insertion of at least one additional amino acid residue within the region 300-311.



46. An enzyme having significant sequence similarity to DAOCS, wherein the penicillin/cephalosporin binding site of DAOC is modified and at least one additional amino acid residue is inserted within the region 300-311.

47. The enzyme of claim 15, further comprising the insertion of at least one additional amino acid residue within the region 300-311.

48. An enzyme having significant sequence similarity to DAOCS, wherein both side chain and the penicillin/cephalosporin binding site of DAOC are modified and at least one additional amino acid residue is inserted within the region 300-311.

49. An enzyme according to claim 13 which is a modification of DAOCS or DACS or DAOC/DACS.

50. An enzyme according to claim 15 which is a modification of DAOCS or DACS or DAOC/DACS.

51. An enzyme as claimed in claim 13, wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

52. An enzyme as claimed in claim 14, wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

53. An enzyme as claimed in claim 49, wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

54. An enzyme as claimed in claim 15, wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

55. An enzyme as claimed in claim 37, wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

56. An enzyme as claimed in claim 38, wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

57. An enzyme as claimed in claim 39, wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

58. An enzyme as claimed in claim 40, wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

59. An enzyme as claimed in claim 41, wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

60. An enzyme as claimed in claim 42, wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

61. An enzyme as claimed in claim 43, wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

62. An enzyme as claimed in claim 44, wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

63. An enzyme as claimed in claim 45, wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

64. An enzyme as claimed in claim 46, wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

65. An enzyme as claimed in claim 47, wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

66. An enzyme as claimed in claim 48, wherein two or more complementary mutations are introduced to create or delete a binding interaction, including H-bonds, electrostatic, or hydrophobic interactions.

67. A polynucleotide encoding for the enzyme of claim 13.

68. A polynucleotide encoding for the enzyme of claim 14.

69. A polynucleotide encoding for the enzyme of claim 49.

70. A polynucleotide encoding for the enzyme of claim 15.

71. A polynucleotide encoding for the enzyme of claim 16.

72. A polynucleotide encoding for the enzyme of claim 37.

73. A polynucleotide encoding for the enzyme of claim 38.

74. A polynucleotide encoding for the enzyme of claim 39.

75. A polynucleotide encoding for the enzyme of claim 40.

76. A polynucleotide encoding for the enzyme of claim 41.

77. A polynucleotide encoding for the enzyme of claim 42.

78. A polynucleotide encoding for the enzyme of claim 43.

79. A polynucleotide encoding for the enzyme of claim 44.

80. A polynucleotide encoding for the enzyme of claim 45.

81. A polynucleotide encoding for the enzyme of claim 46.

82. A polynucleotide encoding for the enzyme of claim 47.

83. A polynucleotide encoding for the enzyme of claim 48.

84. A polynucleotide encoding for the enzyme of claim 50.

85. A polynucleotide encoding for the enzyme of claim 51.

86. A polynucleotide encoding for the enzyme of claim 52.

87. A polynucleotide encoding for the enzyme of claim 53.

88. A polynucleotide encoding for the enzyme of claim 54.

89. A polynucleotide encoding for the enzyme of claim 55.

90. A polynucleotide encoding for the enzyme of claim 56.

91. A polynucleotide encoding for the enzyme of claim 57.

92. A polynucleotide encoding for the enzyme of claim 58.

93. A polynucleotide encoding for the enzyme of claim 59.

94. A polynucleotide encoding for the enzyme of claim 60.

95. A polynucleotide encoding for the enzyme of claim 61.

96. A polynucleotide encoding for the enzyme of claim 62.

97. A polynucleotide encoding for the enzyme of claim 63.

98. A polynucleotide encoding for the enzyme of claim 64.

99. A micro-organism capable of expressing the polynucleotide of claim 67 under fermentation conditions.

100. A micro-organism capable of expressing the polynucleotide of claim 68 under fermentation conditions.

101. A micro-organism capable of expressing the polynucleotide of claim 69 under fermentation conditions.

102. A micro-organism capable of expressing the polynucleotide of claim 70 under fermentation conditions.

103. A micro-organism capable of expressing the polynucleotide of claim 71 under fermentation conditions.

104. A micro-organism capable of expressing the polynucleotide of claim 72 under fermentation conditions.

105. A micro-organism capable of expressing the polynucleotide of claim 73 under fermentation conditions.

106. A micro-organism capable of expressing the polynucleotide of claim 74 under fermentation conditions.

107. A micro-organism capable of expressing the polynucleotide of claim 75 under fermentation conditions.

108. A micro-organism capable of expressing the polynucleotide of claim 76 under fermentation conditions.

109. A micro-organism capable of expressing the polynucleotide of claim 77 under fermentation conditions.



110. A micro-organism capable of expressing the polynucleotide of claim 78 under fermentation conditions.

111. A micro-organism capable of expressing the polynucleotide of claim 79 under fermentation conditions.

112. A micro-organism capable of expressing the polynucleotide of claim 80 under fermentation conditions.

113. A micro-organism capable of expressing the polynucleotide of claim 81 under fermentation conditions.

114. A micro-organism capable of expressing the polynucleotide of claim 82 under fermentation conditions.

115. A micro-organism capable of expressing the polynucleotide of claim 83 under fermentation conditions.

116. A micro-organism capable of expressing the polynucleotide of claim 84 under fermentation conditions.

117. A micro-organism capable of expressing the polynucleotide of claim 85 under fermentation conditions.

118. A micro-organism capable of expressing the polynucleotide of claim 86 under fermentation conditions.

119. A micro-organism capable of expressing the polynucleotide of claim 87 under fermentation conditions.

120. A micro-organism capable of expressing the polynucleotide of claim 88 under fermentation conditions.

121. A micro-organism capable of expressing the polynucleotide of claim 89 under fermentation conditions.

122. A micro-organism capable of expressing the polynucleotide of claim 90 under fermentation conditions.

123. A micro-organism capable of expressing the polynucleotide of claim 91 under fermentation conditions.

124. A micro-organism capable of expressing the polynucleotide of claim 92 under fermentation conditions.

125. A micro-organism capable of expressing the polynucleotide of claim 93 under fermentation conditions.

126. A micro-organism capable of expressing the polynucleotide of claim 94 under fermentation conditions.

127. A micro-organism capable of expressing the polynucleotide of claim 95 under fermentation conditions.

128. A micro-organism capable of expressing the polynucleotide of claim 96 under fermentation conditions.

129. A micro-organism capable of expressing the polynucleotide of claim 97 under fermentation conditions.

130. A micro-organism capable of expressing the polynucleotide of claim 98 under fermentation conditions.

131. The method of using the micro-organisms of claim 99 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

132. The method of using the micro-organisms of claim 100 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

133. The method of using the micro-organisms of claim 101 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

134. The method of using the micro-organisms of claim 102 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

135. The method of using the micro-organisms of claim 103 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

136. The method of using the micro-organisms of claim 104 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

137. The method of using the micro-organisms of claim 105 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

138. The method of using the micro-organisms of claim 106 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

139. The method of using the micro-organisms of claim 107 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

140. The method of using the micro-organisms of claim 108 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

141. The method of using the micro-organisms of claim 109 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

142. The method of using the micro-organisms of claim 110 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

143. The method of using the micro-organisms of claim 111 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

144. The method of using the micro-organisms of claim 112 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

145. The method of using the micro-organisms of claim 113 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

146. The method of using the micro-organisms of claim 114 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

147. The method of using the micro-organisms of claim 115 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

148. The method of using the micro-organisms of claim 116 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

149. The method of using the micro-organisms of claim 117 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

150. The method of using the micro-organisms of claim 118 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

151. The method of using the micro-organisms of claim 119 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

152. The method of using the micro-organisms of claim 120 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

153. The method of using the micro-organisms of claim 121 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

154. The method of using the micro-organisms of claim 122 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

155. The method of using the micro-organisms of claim 123 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

156. The method of using the micro-organisms of claim 124 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

157. The method of using the micro-organisms of claim 125 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

158. The method of using the micro-organisms of claim 126 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

159. The method of using the micro-organisms of claim 127 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

160. The method of using the micro-organisms of claim 128 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

161. The method of using the micro-organisms of claim 129 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

162. The method of using the micro-organisms of claim 130 for the production of beta-lactams of the penicillin or cephalosporin (including cepham) families.

163. The method of claim 131, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

164. The method of claim 132 wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

165. The method of claim 133, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

166. The method of claim 134, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

167. The method of claim 135, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

168. The method of claim 136, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

169. The method of claim 137, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.



170. The method of claim 138, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

171. The method of claim 139, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

172. The method of claim 140, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

173. The method of claim 141, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

174. The method of claim 142, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

175. The method of claim 143, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

176. The method of claim 144, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

177. The method of claim 145, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

178. The method of claim 146, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

179. The method of claim 147, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

180. The method of claim 148, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

181. The method of claim 149, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

182. The method of claim 150, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

183. The method of claim 151, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

184. The method of claim 152, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

185. The method of claim 153, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

186. The method of claim 154, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

187. The method of claim 155, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

188. The method of claim 156, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

189. The method of claim 157, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

190. The method of claim 158, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

191. The method of claim 159, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

192. The method of claim 160, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

193. The method of claim 161, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

194. The method of claim 162, wherein the micro-organism contains another modified enzyme of the penicillin and cephalosporin biosynthesis pathway.

195. The method of claim 163, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

196. The method of claim 164, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

197. The method of claim 165, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

198. The method of claim 166, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

199. The method of claim 167, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

200. The method of claim 168, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

201. The method of claim 169, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

202. The method of claim 170, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

203. The method of claim 171, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

204. The method of claim 172, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

205. The method of claim 173, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

206. The method of claim 174, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

207. The method of claim 175, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

208. The method of claim 176, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

209. The method of claim 177, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

210. The method of claim 178, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

211. The method of claim 179, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

212. The method of claim 180, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

213. The method of claim 181, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

214. The method of claim 182, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

215. The method of claim 183, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

216. The method of claim 184, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

217. The method of claim 185, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

218. The method of claim 186, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

219. The method of claim 187, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

220. The method of claim 188, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

221. The method of claim 189, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

222. The method of claim 190, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.



223. The method of claim 191, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

224. The method of claim 192, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

225. The method of claim 193, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

226. The method of claim 194, wherein said modified enzyme is isopenicillin N synthase, amidohydrolase/acetyltransferase, or L-delta-(aminoadipoyl)-L-cysteine-D-valine (ACV) synthetase.

227. A method as claimed in claim 22 wherein the said other enzyme is modified, by deletion or addition or alteration; at one or more of the sites selected from the group consisting of Thr72, Arg74, Arg75, Ile88, Glu156, Leu158, Arg160, Arg162, Phe164, Met180, Leu186, Ser187, Thr190, Ile192, Phe225, Pro241, Val245, Val262, Phe264, Arg266, Asp301, Tyr302, Val303, Asn304; Ile305, Arg 306, and Arg307; or using the following information for the design of an inhibitor: Asp185, His183 and His243 act as ligand to the iron; Arg258 and Ser260 and the Fe bind the 2-oxoglutarate; Met180, Phe225, Leu31 and Val245 are close to the iron binding site; Tyr33, Arg160, Arg162, Phe164, Ile192, Gln194, Leu204, Leu223, Leu215 are important for the

construction of the part of the active site binding 2-oxoglutarate; and Arg160 and Arg162 are important for binding an amino acid or peptide derived substrate.

228. A method as claimed in claim 23, wherein the said other enzyme is prolyl 4-hydroxylase, prolyl 3-hydroxylase, aspartyl hydroxylase, or lysyl hydroxylase and the inhibitor is to be used for the treatment of human diseases including fibrotic diseases including liver cirrhosis and arthritis.

229. A method as claimed in claim 23, wherein the said other enzyme is p-hydroxyphenylpyruvate dioxygenase and the inhibitor is to be used in the treatment of certain genetic disorders.

230. A method as claimed in claim 23, wherein the said other enzyme is involved in herbicide resistance and the information is to be used to design new herbicides to overcome the problem of resistance.

231. A polynucleotide encoding for the enzyme of claim 65.

232. A polynucleotide encoding for the enzyme of claim 66.

#### **REMARKS**

Entry of the amendments to the claims before examination of the application is respectfully requested. The claims have been amended for the sake of clarity. No new matter has been added by these amendments. Applicants authorize the Commissioner to charge any